II. REMARKS

Preliminary Remarks:

Entry of the Preliminary Amendment, which claims priority to the filing date of parent application U.S. Serial No. 09/259,338, is acknowledged.

Figure 1 was objected to for informalities. A substitute Figure 1 was submitted with the reply filed on April 11, 2002.

The specification was objected to, because the reference to co-pending applications at page 14, line 3, was incomplete. The paragraph beginning at page 14, line 3, has been amended to properly identify U.S. Serial Nos. 09/259,337 and 09/259,347, which disclose methods for determining percent binding affinity and immunoreactivity of conjugates after labeling.

Claims 1 and 5 are amended, claim 17 is canceled, and new claims 49-61 are added.

Claim 1 is amended to be directed to a method for radiolabeling procedure whereby the chelator-conjugated protein, ligand, or peptide is exposed to a therapeutic radioisotope or a salt thereof for a sufficient amount of time under conditions such that a radiolabeled protein, ligand or peptide having radiochemical purity greater than 95%, sufficient binding specificity, and a specific activity of at least about 5 mCi/mg, is achieved such that the radiolabeled protein, ligand or peptide may be administered directly to the patient without further purification. Support for the disclosed radiolabeling method wherein radiochemical purity greater than 95 % is achieved is found in the specification, for example, at page 17, lines 27-29, and page 28, lines 15-17, as well as in original claim 17 (now canceled). Support for the claimed method wherein a specific activity of at least about 5 mCi/mg is achieved can be found in the application, for example at page 13, lines 14-16, and in original claim 19 (now canceled).

Claim 5 is amended to be directed to the method of claim 1, wherein said protein or peptide is an antibody or antibody fragment, support for which is found in original claim 1.

New claims 49-51 are directed to the method of claim 1, wherein the incubation time is about three minutes, five minutes, and ten minutes, respectively, support for which is found

in the specification for example, in Table 3 on page 26. New claims 52-55 are directed to the disclosed method for radiolabeling wherein the level of radioincorporation that is achieved is at least about 96%, 97%, 98% and 99%, respectively, support for which is found in the specification, for example, in Tables 1-3, 6, and 7 on pages 24-26 and 35-37. New claims 57 and 58 are directed to the disclosed method for radiolabeling wherein the protein or peptide is a therapeutic antibody or antibody fragment such as a therapeutic antibody or antibody fragment that binds specifically to CD20, support for which is found in the specification, for example, on page 17, lines 1-18. New claims 56 and 59 are directed to the disclosed method for radiolabeling wherein the protein or peptide is an antibody fragment selected from the group consisting of Fab, $F(ab')_2$, and Fv fragments, support for which is found in the specification, for example, on page 10, lines 18-21. New claims 60 and 61 are directed to the disclosed method for radiolabeling wherein the binding specificity of the radiolabeled product is at least 50% or at least 80%, respectively, support for which is found in the specification, for example, at page 14, lines 1-2, and in Table 2 on page 25.

Patentability Remarks

35 U.S.C. §112, Second Paragraph

Claims 1-19 were rejected under 35 U.S.C. § 112, second paragraph, because the terms "ligand" and "the radiolabelled antibody" lack antecedent basis. Office Action, at page 2, ¶ 4-6. Claim 1 is amended to provide proper antecedent basis for each term in the claim, and is believed to comply with the requirements of 35 U.S.C. § 112, second paragraph.

Claim 18 was also rejected under 35 U.S.C § 112, second paragraph, as being allegedly indefinite because it is unclear as to what binding specificity is 100%. Office Action, at page 2, ¶ 7. This rejection is respectfully traversed. Applicant submits that the term "binding specificity" is understood in the art to represent the percentage of labeled antibody that binds to a target antigen (*i.e.*, CD20) relative to binding of the same antibody to a non-specific antigen. The subject application uses the term "binding specificity" according to this art-recognized definition. For example, the application as originally filed describes

performance of a binding assay using cells that express or do not express target antigen (page 22, line 9, through page 23, line 3). The binding results are expressed in Table 1 (page 24), Table 2 (page 25), and Table 3 (page 26). Thus, claim 18 is believed to particularly point out and distinctly claim the present invention in compliance with the requirements of 35 U.S.C. § 112, second paragraph. Accordingly, the applicant respectfully requests that the rejection of claims under 35 U.S.C. § 112, second paragraph, be withdrawn.

35 U.S.C. §102(b) and 102(e)

Claims 1-5, 8, 10-14, and 17-18 were rejected under 35 U.S.C. § 102(b) as being anticipated by Mather et al. (1989) *Eur J Nucl Med* 15:307. Office Action, at page 3, ¶ 3, through page 4, ¶ 2. Mather et al. describes preparation of ^{90}Y-labeled antibodies that can be administered to a patient in the absence of post-labeling purification. Although Mather et al. recognizes radiolysis of the labeled antibodies that results in sub-optimal *in vivo* results, the office action contends that the properties of "sufficient purity, specific activity, and binding specificity" require quantitative values to distinguish the present invention over the prior art. As amended, claim 1 is directed to a method for radiolabeling that produces a radiolabeled protein, ligand or peptide having radiochemical purity greater than 95% and a specific activity of at least about 5 mCi/mg. The Mather et al. reference states (p. 311) that, using the radiolabeling method it discloses, "[h]igh labelling efficiencies were only achievable at the relatively low specific activity of 1 mCi/mg;" and Fig. 1 (p. 308) shows that ^{90}Y-labeled antibodies labeled to specific activity of 5 mCi/mg by the radiolabeling method of Mather et al. have radiochemical purity of no more than about 65 %. In view of the foregoing, the pending claims are believed to be patentably distinguished over the Mather et al. reference, and the applicant respectfully requests that the rejection of claims under 35 U.S.C. § 102(b) as anticipated by Mather et al. be withdrawn.

Claims 1, 8, 10-14, and 17-18 were rejected under 35 U.S.C. § 102(b) as anticipated by Richardson et al. (1987) *Nucl Med Commun* 8:347 ("Richardson"), which describes radiolabeling of antibodies with ^{111}Indium. This rejection is respectfully traversed.

As noted in the application as originally filed, methods for radiolabeling antibodies for diagnostic applications are inadequate for preparation of therapeutic radioconjugates. In particular, prolonged duration of labeling reactions can cause significant radiolysis of an antibody or protein labeled with high energy radioisotopes suitable for therapeutic applications. Claim 1 is amended to include the term "therapeutic" to describe "radioisotope" in step (i). As such, claim 1 is believed to be patentably distinguished over Richardson, which only describes preparation of radioconjugates useful for diagnosis. Claims that depend from claim 1 and are also believed to be patentably distinguished over Richardson. Applicant therefore respectfully requests withdrawal of the rejection of claims based on Richardson.

Claims 1-5, 8, 10-11, and 17 were rejected under 35 U.S.C. § 102(b) as allegedly anticipated by Chinol et al. (1987) *J Nucl Med* 28:1465 ("Chinol") in light of Hnatowich et al. (1983) *J Immunol Meth* 65:147 ("Hnatowich"). Chinol describes preparation of ^{90}Y-labeled antibodies using methods according to Hnatowich. The office action states that HPLC steps conducted after labeling were for the purpose of analyzing radiochemical purity (citing the paragraph of Chinol spanning pages 1469-1470), and that purification is therefore not a prerequisite to *in vivo* use. Office Action, at page 5, ¶ 2-5.

As in Mather, the radiolabeling methods of Chinol yield antibodies having only modest specific activity (1-3 mCi/mg) which have little clinical value. Claim 1 is amended to recite a radiolabeled protein, ligand or peptide "having a specific activity of at least about 5 mCi/mg." The applicant submits that the method of claim 1 is patentably distinguished from Chinol. Claims that depend from claim 1 and are also believed to be patentably distinguished over Chinol. The applicant respectfully requests that the rejection of claims under 35 U.S.C. § 102(b) based on Chinol be withdrawn.

Claims 1-3, 5, 17 and 19 are rejected under 35 U.S.C. § 102(b) or § 102(e) as allegedly anticipated by U.S. Patent No. 5,942,210 ("the '210 patent," also PCT International Publication No. WO 96/14879). In particular, the Examiner contends that the '210 patent teaches preparation of antibodies labeled with a therapeutic radioisotope. Office Action, at

page 5, ¶ 6 through page 6, ¶ 5. Applicant respectfully traverses this rejection. The '210 patent describes a "one-pot" method for radiolabeling that involves labeling of a lyophilized conjugate/transchelator/reducing agent mixture via addition of a solution containing the isotope. ^{99}Tc-labeled antibodies having high specific activity were prepared using the one-pot method and administered to test animals, apparently without a prior purification step. The office action states that the '210 patent also teaches preparation of therapeutic radioconjugates comprising rhenium. Office Action, at page 6, ¶ 2.

Applicant submits that the office action has erroneously interpreted the disclosure of the '210 patent. As set forth in the Declaration under 37 C.F.R. § 1.132 of Dr. Paul Chinn, a copy of which is attached to the reply filed April 11, 2003, the radiolabeling methods of the '210 patent are unsuitable for preparing radiolabeled conjugates useful for therapy, *i.e.* conjugates that include high energy metallic isotopes such as ^{90}Y. Contrary to the suggestion of the Examiner, the '210 patent suggests, but does not show, preparation of therapeutic radioconjugates. Absent any supporting experimental results, a skilled artisan would find the suggested method implausible.

Claim 1 is amended to include the term "therapeutic" to describe "radioisotope" in step (i). The radiolabeling methods of the present application can be used to prepare radiolabeled proteins, ligands, or peptides having high specific activity. In contrast to the radiolabeling methods of the '210 patent, the methods of the present disclosure include the use of a high energy metallic radioisotope, ^{90}Y, whereby the resultant radioconjugate is suitable for therapeutic administration to a subject in the absence of a purification step.

Based on the foregoing, claim 1 is believed to be patentably distinguished over the '210 patent (Ultee). Claims that depend from claim 1 and are also believed to be patentably distinguished over the '210 patent. The applicant therefore respectfully requests that the rejection of claims under 35 U.S.C. § 102(b) and/or 102(e) based on the '210 patent be withdrawn.

Conclusion

All objections and rejections having been addressed, it is respectfully submitted that the present application is in condition for allowance and a Notice to that effect is earnestly solicited. If any points remain in issue, which the Examiner feels may be best resolved through a personal or telephone interview, he is kindly requested to contact the undersigned attorney at the telephone number listed below.

Respectfully submitted,

PILLSBURY WINTHROP LLP

By: _____ Reg 37,087
Thomas A. Cawley, Jr., Ph.D.
Reg. No.: 40,944
Tel. No.: (703) 905-2144
Fax No.: (703) 905-2500

TAC/CR
1600 Tysons Boulevard
McLean, VA 22102
(703) 905-2000

Attachments

Attached hereto are:

(i) a copy of a § 1.132 Affidavit of Dr. Paul Chinn;

(ii) an Application Data Sheet pursuant to 37 C.F.R. § 1.76.